

## Remarks

### I. Status of the Application and Claims

No claims were cancelled or added herein. The claims presently under consideration are claims 5-24.

### II. The Amendments

No amendments have been made herein.

## The Rejections

The Examiner has maintained a rejection of all pending claims as being obvious over Dormoy, et al. (*Synthesis*, pg. 81-86 (1996)), in view of Carlsen, et al., (*J. Org. Chem.* 46:3936-3938 (1981)) and Riley, et al. (*J. Chem. Soc., Chem. Commun.*, 1530-1532 (1983)) and further in view of Narukawa, et al. (*Tetrahedron* 53:539-556 (1997)).

Applicants have traversed this rejection.

In the present Response, Applicants are submitting a Declaration Under 37 CFR §1.132, by Dr. Günter Knaup as evidence for the nonobviousness of the pending claims. Dr. Knaup is Director of Process Research at Evonik Degussa GmbH (the assignee of the present application) and is responsible for process development for, *inter alia*, 4-ketoproline derivatives. He has the equivalent of a Ph.D. in chemistry and has conducted research in the area of organic chemistry for more than 25 years. Dr. Knaup reviewed the Office Actions for the above application that were sent on April 21, 2008 and February 18, 2010. In addition, he reviewed the references that have been used in rejecting claims.

In paragraph 4 of the Declaration, Dr. Knaup states that, in his opinion, the references cited in the Office Action do not contain teachings that would provide one of skill in the art of organic chemistry with a reasonable expectation that the process claimed by Applicants would succeed. The basis for this conclusion is set out in subparagraphs a-e as follows:

In subparagraph a, Dr. Knaup states that Dormoy teaches that N-protected ketoproline esters can be prepared by oxidation of the corresponding N-protected hydroxyproline esters

using sodium metaperiodate and ruthenium dioxide. He points out that Dormoy uses a biphasic system consisting of tetrachloromethane and water and does not suggest that the reaction could be run in an aqueous one phase system alone. The reaction is carried out in the presence of strong oxidizing agents and, to maintain compound stability, Dormoy uses a biphasic system to withdraw the oxidation product from the aqueous phase containing oxidizing agent into an organic phase. In contrast, Applicants' procedure reduces the need for organic solvents and yields a pure reaction product without the need for an extraction. Dr. Knaup concludes that processes such as that described by Dormoy cannot provide a reasonable expectation that the process claimed by Applicants would succeed.

In subparagraph b, Dr. Knaup states that Carlsen teaches that oxidations using ruthenium dioxide and periodate usually failed when carboxylic acids are present or generated during the reaction but that this problem can be solved by adding acetonitrile as a co-solvent. Nevertheless, Carlsen, like Dormoy, used a standard biphasic system consisting of tetra-chloromethane and water. Dr. Knaup states that Carlsen, taken alone or in combination with Dormoy, would not suggest to a skilled artisan carrying out oxidations in the manner claimed by Applicants.<sup>1</sup> In addition, Dr. Knaup suggests that Carlsen seems contradictory to Narukawa (discussed further below) which presents results suggesting that acids may not have a negative effect on oxidations performed using the ruthenium oxide/periodate system.

Subparagraph c of the Declaration states that Riley teaches the catalytic oxidation of tert.-amines with molecular oxygen in a homogenous aqueous solution to produce the corresponding N-oxide. However, Dr. Knaup states that N-protected hydroxyprolines, *i.e.*, the substrate of the process according to the present invention, are not tertiary amines and, from a chemist's point of view, the substrates disclosed in Riley are completely different from N-protected hydroxyprolines. In addition, the products obtained by Riley (N-oxides) are not ketoproline compounds and ketoproline compounds are not encompassed by the term "N-oxides." Dr. Knaup indicates that the reasons for the superior results of Riley using water as solvent were associated with the stabilizing effects of water on the N-oxide products and that

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<sup>1</sup> Applicants claims require oxidation in an aqueous one-phase system. The oxidation product is induced to crystallize out during the addition of oxidizing agent and not extracted in the manner of Dormoy and Carlsen.

a similar effect on ketoprolines does not exist and was never proposed. Based on these considerations, Dr. Knaup concludes that Riley reference is not relevant to the present invention either taken alone or in combination with the other references cited by the Examiner.

In subparagraph d, Dr. Knaup indicates that Narukawa teaches the oxidation of tert.-butoxycarbonyl-4-hydroxyproline with sodium metaperiodate and ruthenium oxide using a biphasic solvent system consisting of water and ethyl acetate. He states that it cannot be concluded from this publication that the product tert.-butoxycarbonyl-4-oxoproline is not largely soluble in water. Although the extraction of product from the aqueous layer in a twofold extraction with ethyl acetate is described, this just indicates that the product is reasonably soluble in water, thus requiring a second extraction step to be removed completely. Therefore, Narukawa does not suggest that Applicant's process might work. In addition, Dr. Knaup points out that ketoproline compounds are amino acid derivatives and such compounds generally show good solubility in water or aqueous solutions. Thus, a person skilled in the art would expect good water solubility for ketoproline compounds rather than low water solubility.

In subparagraph e, Dr. Knaup summarizes his conclusions. In particular, he states that Dormoy and Carlson only disclose extractions in a biphasic system, whereas the process of the present invention does not require a complicated extraction process for removal of the reaction product from the oxidation system. Possible further oxidation of the reaction product and formation of byproducts is avoided in a simple and, in view of Dormoy and Carlsen, unexpected manner. Although Riley carries out an oxidation in an aqueous one phase system, neither the starting substances nor the end products in this reference are comparable to hydroxyproline or ketoproline. Therefore, Riley cannot provide a reasonable expectation that the process claimed in the present application will succeed. In addition, Riley does not carry out a crystallization and therefore does not address the problem of how the formation of byproducts could be avoided. Finally, Dr. Knaup states that, like Dormoy and Carlson, Narukawa only teaches the use of biphasic systems. Regarding the solubility of ketoproline, the only teaching, if any, that may be present is that ketoprolines have reasonably good solubility in water and therefore do not precipitate easily.

Based upon the above considerations, Dr. Knaup concludes that, in his opinion, one of skill in the art could not have reasonably predicted the success of the reaction of the present claims based upon the combination of Dormoy, Carlsen, Riley and Narukawa.

Applicants submit that the Declaration provides additional support for the arguments that have been made in favor of the nonobviousness of the present claims. The combined references do not teach a reaction performed in a one phase system where compounds are stabilized against further oxidation by crystallization performed concurrently with the addition of reagent.

### Conclusion

In light of the discussion above, Applicants respectfully submit that a prima facie case of obviousness has not established. It is therefore requested that the rejection of claims be withdrawn and that the present application be passed to allowance.

If, in the opinion of the Examiner, a phone call may help to expedite the prosecution of this application, the Examiner is invited to call Applicants' undersigned attorney at (240)683-6165.

Respectfully submitted,  
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